Docket No. 7732-022-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: MICHAEL CLIMO, ET AL. GAU: 1633
SERIAL NO: 09/120,030 EXAMINER: BORIN, M.
FILING DATE: JULY 21, 1998
FOR: METHOD FOR THE TREATMENT OF STAPHYLOCOCCAL DISEASE

DECLARATION UNDER 37 C.F.R. § 1.132

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

I, Michael Climo, M.D., do hereby declare and state that:

1. I am one of the inventors of the subject matter claimed in the above-identified application and one of the inventors named in the above-identified application. I am a resident and citizen of the United States of America. I am not an employee of AMBI Inc., whom I understand to be the assignee of the above-referenced patent application, nor do I have any financial interest in the issuance of the above-referenced application as a patent.

2. I have reviewed the above-identified application, together with the presently pending claims. As I understand it, the subject matter claimed in the application is directed to compositions and methods for treating staphylococcal infections. The method comprises administering an effective amount of at least one recombinantly produced lysostaphin analogue. The composition comprises at least one recombinantly produced lysostaphin analogue and a pharmaceutically acceptable carrier. The recombinantly produced lysostaphin analogue has the biological activity of proteolytic attack against glycine-containing bridges in the cell wall of peptidoglycan of staphylococci.

3. I am aware of the rejection of Claims 4-5 and 28-29 under 35 U.S.C. §103(a) issued in the above-identified application in an Office Action dated June 4, 2001. In essence, the Examiner asserts that the invention claimed in these claims is obvious over Zygmunt et al., *Fortschr. Armzneimittelforsch.*, 16:309-333 or Stark et al., *N.Engl.J.Med.*, 291:239-240 or Goldberg et al., *Antimicrob. Ag. Chemother.*, 45-53 in view of Oldham et al., *J. Dairy Sci.*, 74:4175-4182.

4. I am also aware of the rejection of Claims 32 and 35 under 35 U.S.C. §103(a) issued in the above-identified application in the same Office Action where the Examiner asserts that the invention claimed in Claims 32 and 35 is unpatentable over Zygmunt et al. or Stark et al. or Goldberg et al. in view of Oldham et al. and further in view of Dixon et al., *Yale J. Biol. Med.*, 41:62-68.

5. In addition, I am aware of the rejection of Claims 33-34 and 36-55 under 35 U.S.C. §103(a) also issued in the above-identified application in the same Office Action. In essence, the Examiner asserts that the invention claimed in these claims is obvious over Zygmunt et al. and Stark et al. and Goldberg et al. and Oldham et al.

6. I have reviewed the cited reference to Zygmunt et al. Zygmunt et al. review the properties and biological activity of lysostaphin and indicate that lysostaphin is effective against staphylococcal infection in various animal models including dogs and mice.

7. I have also reviewed the cited reference to Stark et al. Stark et al. disclose treatment with a single, 500 mg dose of lysostaphin.

8. I have also reviewed the cited reference to Goldberg et al. in which Goldberg et al. discusses the treatment of experimental staphylococcal endocarditis in dogs with lysostaphin. Goldberg et al. noted that the "preliminary observations have established efficacy of lysostaphin in the early period of experimental canine endocarditis." See Goldberg et al., page 52 (emphasis

added).

9. Furthermore, Goldberg et al. teach the use of lysostaphin in the treatment of experimental canine endocarditis. This disclosure cannot be extrapolated to treatment of humans. Nor is it predictive of the efficacy of treatment in humans. This disclosure is, therefore, of limited utility in assessment of the administration of lysostaphin to humans. Unlike Applicants' present invention, therefore, Goldberg et al. fail to demonstrate eradication of a staphylococcal infection in humans. Additionally, high doses of lysostaphin were only moderately effective, as judged by the health of the dogs and by the extent of reduction in the number of bacteria in the heart valves and kidneys.

10. Both Stark et al. and Goldberg et al. are pre-1975 studies. Neither teaches or suggests that lysostaphin is effective as routine bactericide treatment in humans for systemic staphylococcal infection.

11. I have also reviewed the cited reference to Oldham et al. Oldham et al. disclose the use of recombinant lysostaphin as a "potential intramammary therapeutic" in treating bovine mastitis. See Abstract. Indeed, beginning at page 4180, Oldham et al. provide a detailed disclosure of the unusual circumstances involved in mastitis treatment, including the effect of milk on the activity of recombinant lysostaphin and the possible reasons for this effect. In the right-hand column of page 4180, the authors state that understanding the basis of reduced activity of recombinant lysostaphin in their system is essential for targeting proper therapeutic formulations. This disclosure cannot be extrapolated to treatment of humans. Unlike Applicants' present invention, therefore, Oldham et al. fail to demonstrate eradication of staphylococcal infections in humans.

12. Moreover, Oldham et al. teach only localized treatment, namely injection into the teat canal. See, e.g., Abstract. One of skill in the art would recognize that non-systemic use of recombinant lysostaphin in a non-human model is not predictive of systemic use in humans.

13. On pages 4181-4182, Oldham et al. contrast the localized treatment of bovine mastitis with previous lysostaphin studies. The authors first note that "work with nonrecombinant purified lysostaphin was reported to generate immunological problems after therapy." See Oldham, page 4181. The authors then note that while "intramammary administration to the bovine . . . [was] relatively nonimmunogenic," recombinant lysostaphin "is highly immunogenic when administered to some species parenterally in adjuvant." See Oldham, page 4182. One of ordinary skill in the art would instantly recognize, therefore, that such a highly immunogenic protein is eminently unsuitable for systemic use, which is the use ascribed to the present invention.

14. The combined teachings of the above-referenced articles would not lead one of skill in the art to produce a composition for systemically treating staphylococcal infections in humans comprising a recombinantly produced lysostaphin analogue, especially in dosage amounts less than 50 mg/kg.

15. Moreover, based on the above-referenced articles to Zygmunt et al., Stark et al., Goldberg et al., Oldham et al. and Dixon et al., one of ordinary skill in the art would not be motivated to systemically treat humans having staphylococcal infections with a recombinantly produced lysostaphin analogue.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed true. Further, I am aware that willful false statements and the like are punishable by fine or imprisonment or both, 18 U.S.C. § 1001, and that such willful false

statements may jeopardize the validity of the above-identified patent application and any patent to issue thereon.

DATE: 9/27/01

Michael Climo, M.D.